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Hemostatic Molecular Markers Before the Onset of Disseminated Intravascular Coagulation

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We retrospectively measured various hemostatic markers in 240 patients with disseminated intravascular coagulation (DIC) before the onset of DIC and in 110 non-DIC patients, and examined their usefulness for the diagnosis of pre-DIC. Changes in prothrombin time ratio and fibrinogen levels were not significant before the onset of DIC. The plasma levels of fibrinogen and fibrin degradation products before the onset of DIC were increased and the platelet count was gradually reduced in nonleukemic patients; these changes were already significant in the non-DIC state. The plasma levels of thrombin–antithrombin complex (TAT), plasmin–plasmin inhibitor complex (PPIC), D-dimer, and soluble fibrin monomer (sFM) were increased before the onset of DIC. In leukemic patients, the plasma levels of sFM on day 5, those of TAT on day 3, and D-dimer on day 1, were significantly increased before the onset of DIC. The levels of most hemostatic markers 7 days before the onset of DIC were not different from those observed in the non-DIC state. In nonleukemic patients, only D-dimer, sFM, and TAT levels were significantly increased 7 days before the onset of DIC compared with values in the non-DIC state. The positive rate of hemostatic markers for the diagnosis of DIC, TAT, and PPIC were high during the pre-DIC and non-DIC groups. The plasma levels of sFM and D-dimer were low in non-DIC and increased gradually during the pre-DIC state. These findings suggest that hemostatic molecular markers such as sFM, D-dimer, and TAT are useful for the diagnosis of pre-DIC, although their cutoff values were different among various diseases. Am. J. Hematol. 60:273–278, 1999. © 1999 Wiley-Liss, Inc.

Key words: DIC; pre-DIC; hemostatic molecular markers; soluble fibrin monomer; D-dimer

INTRODUCTION

Disseminated intravascular coagulation (DIC) [1,2] is often observed in patients with leukemia, solid cancers, and infection, and is frequently accompanied by severe bleeding and organ failure. In Japan, most patients with DIC are treated with heparin, antithrombin concentrate, or gabexate mesilate (FOY), a synthetic proteinase inhibitor [3] that inhibits the activity of thrombin, factor Xa, plasmin, and plasma kallikrein. However, the efficacy of these anticoagulant agents has not been satisfactory [3–6]. In our previous study, we found that much more efficacy can be achieved if the treatment is started in the pre-DIC state than in established DIC. The outcome was poorer with increasing DIC score, suggesting that early diagnosis and early treatment are important [6]. In Japan, DIC is diagnosed based on the presence of underlying disease, bleeding symptoms, thrombosis-induced organ failure, and on the values of prothrombin

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TABLE I. Subjects*

	Pre-DIC → DIC	Non-DIC	Total
Leukemia	114	61	175
ALL	29	6	35
AML	22	14	36
APL	18	10	28
AMMoL	6	14	20
CMLbc	9	3	12
MDS	2	3	5
NHL	19	5	24
Others	9	6	15
Cancer	65	21	86
Stomach	21	8	29
Lung	13	5	18
Pancreas	7	2	9
Prostate	5	1	6
Liver	4	1	5
Others	15	4	19
Infection	42	23	65
Sepsis	24	13	37
Pneumonia	12	7	19
Others	6	3	9
Others	19	15	34
Total	240	110	360

*DIC, disseminated intravascular coagulation; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; AMMoL, acute myelomonocytic leukemia; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndromes; NHL, non-Hodgkin's lymphoma.

time (PT), fibrinogen, fibrin degradation products (FDP), and platelet counts [7,8]. Fibrin D-dimer [9], Thrombin-antithrombin complex (TAT) [10], plasmin–plasmin inhibitor complex (PPIC) [11], prothrombin fragment 1+2 [12], and soluble fibrin monomer (sFM) [13], which are sensitive indicators of coagulation activation or secondary fibrinolysis, recently have been shown to be helpful for the diagnosis of DIC and thrombotic diseases. It is now also possible to measure plasma levels of thrombomodulin (TM) [14], tissue factor (TF) [15], tissue type plasminogen activator (t-PA), plasminogen activator inhibitor-I (PAI-I) [16], and von Willebrand factor (vWF), all of which are released from vascular endothelial cells.

In this study, we measured retrospectively various hemostatic markers before the onset of DIC in patients, and examined their usefulness for the diagnosis of pre-DIC.

MATERIAL AND METHODS

This study comprised 240 DIC patients with samples collected in the pre-DIC state and 110 non-DIC patients with the same underlying diseases as the patients with DIC (175 with leukemia, 86 with solid cancers, 65 with infections, and 34 other diseases [Table I]). The diagnosis of DIC was based on a modified version of the criteria established by the Japanese Ministry of Health and Welfare [7,8], and pre-DIC was defined as the condition that was present 1 week before the onset of DIC [8]. Organ failure was considered to occur in the lung when the PaO2 was 50 mmHg or less at room air; in the kidney when creatinine was 3 mg/dl or more; when symptoms of shock from heart failure were present; and when the patient was in a coma or responded only to pain. Hemostatic examinations were performed retrospectively 7, 5, 3, 1 and 0 days before the onset of DIC.

Activated partial thromboplastin time (APTT), PT, fibrinogen, fibrin, and FDP were measured as described previously [17]. Plasma protein C antigen and protein S antigen were measured by enzyme-linked immunosorbent assays (ELISA), using anti-protein C polyclonal antibody (Dakopatts, Hagersten, Denmark) and anti-protein S polyclonal antibody (Dakopatts). Plasma levels of TAT, PPIC, D-dimer, and sFM were determined using Enzygnost TAT (Behringwerke AG, Marburg, Germany), PIC-test (Teijin, Tokyo, Japan), Flelisa D-dimer (Agen, Brisbane, Australia), and Enzymun FM test (Boehringer Mannheim GmbH, Mannheim, Germany), respectively. Antithrombin and protein C activities were measured by an amidolytic assay, using Berichrom-Antithrombin (Behringwerke AG) and Berichrom-Protein C (Behringwerke AG), respectively. Plasma thrombomodulin, TF, and PAI-I levels were measured by TM ELISA kit (Fuzirebio LTD, Tokyo, Japan), TF kit (ADI), and Imulyse™ PAI-I (Biopool AB, Umea, Sweden), respectively.

Hemostatic markers were considered to be positive for the diagnosis of DIC when the following data were present: Platelet count $<8.0 \times 10^4/\mu l$ FDP >10 μg/ml, fibrinogen level <150 mg/dl, PT ratio >1.24, TAT level >15 ng/ml, sFM >100 μg/ml, PPIC >1.5 μg/ml, and D-dimer >2,000 ng/ml. Positive rate (%) = number of positive patients/total number of patients. The data are expressed as mean ± standard deviation (SD) and statistical analysis was performed using the Wilcoxon test and the Student's *t*-test. *P* values of <0.05 were considered as statistically significant.

RESULTS

Changes in PT ratio were not significant in nonleukemic patients, but they were significant in leukemic patients 1 day before the onset of DIC. Plasma fibrinogen levels were significantly reduced 1 day before the onset of DIC in leukemic patients, and 5 days before the onset of DIC in nonleukemic patients but these levels were higher than the normal range. Plasma FDP levels before the onset of DIC were slightly high in leukemic patients or moderately high in nonleukemic patients; these levels were significantly high at the onset of DIC. Platelet count did not change in leukemic patients, but it was gradually reduced in nonleukemic patients. Plasma antithrombin levels did not change in either group of patients in pre-

TABLE II. Hemostatic Markers in Pre-DIC†

		Day before DIC				
		−7	−5	−3	−1	0
PT Ratio	L	1.10 ± 0.12	1.09 ± 0.10	1.11 ± 0.12	1.30 ± 0.31**	1.31 ± 0.30**
	N	1.16 ± 0.17	1.21 ± 0.19	1.30 ± 0.58	1.22 ± 0.30	1.39 ± 0.42**
Fibrinogen (mg/dl)	L	326 ± 165	318 ± 167	303 ± 147	236 ± 148**	206 ± 133**
	N	321 ± 164	292 ± 142*	288 ± 159**	284 ± 166**	253 ± 170**
FDP (μg/ml)	L	11.1 ± 7.0	13.2 ± 7.9	12.8 ± 8.8	14.4 ± 9.4	41.0 ± 34.7**
	N	29.0 ± 34.0	27.0 ± 31.5	25.9 ± 25.2	28.9 ± 39.3	41.0 ± 34.7**
Platelet ($\times 10^4/\mu l$)	L	5.5 ± 4.8	6.7 ± 5.9	6.6 ± 9.2	5.4 ± 3.2	5.2 ± 5.3
	N	17.7 ± 10.6	14.0 ± 7.7*	13.3 ± 8.3**	12.1 ± 7.2**	7.9 ± 6.3**
Antithrombin (%)	L	87.2 ± 26.3	86.6 ± 20.0	88.9 ± 17.8	75.7 ± 22.7	81.9 ± 24.2
	N	77.4 ± 24.0	75.5 ± 31.1	69.0 ± 23.2	78.6 ± 23.2	65.0 ± 25.6*

†DIC, disseminated intravascular coagulation; PT, prothrombin time; FDP, fibrin degradation products; L, leukemia; N, nonleukemia.
*$P < 0.05$.
**$P < 0.01$ compared with −7 day.

DIC; however, at the onset of DIC, their levels were significantly reduced in nonleukemic patients (Table II). Plasma D-dimer, sFM, TAT, and PPIC levels were increased before the onset of DIC. In leukemic patients, the plasma levels of sFM on day 5, those of TAT on day 3, and D-dimer on day 1, were significantly increased before the onset of DIC. In nonleukemic patients, the plasma levels of sFM were significantly increased on day 1 before the onset of DIC (Table III). The plasma levels of TF and PAI-I did not change significantly before the onset of DIC, and those of TM were markedly increased 1 day before the onset of DIC (Table IV). The PT ratio, and the plasma levels of fibrinogen, FDP, antithrombin, D-dimer, PPIC, and the platelet count 7 days before the onset of DIC were not different from those observed in the non-DIC state. In nonleukemic patients, only the plasma levels of D-dimer, sFM, and TAT were significantly increased 7 days before the onset of DIC as compared with values observed in non-DIC state (Table V).

Regarding the positive rate of hemostatic markers for the diagnosis of DIC, FDP was already high in non-DIC, and PT ratio and fibrinogen were low before the onset of DIC. In the nonleukemic group, the positive rate of FDP was high in pre-DIC, DIC, and non-DIC states. The positive rate of the platelet count was slightly high before the onset of DIC, but it was moderately high in non-DIC. Fibrinogen and the PT ratio were very low in non-DIC, but they were increased slightly during the pre-DIC state (Fig. 1A). The positive rate of TAT and PPIC was high during the pre-DIC and non-DIC states. The positive rate of sFM and D-dimer was low in non-DIC and increased gradually during the pre-DIC state (Fig. 1B).

DISCUSSION

In Japan, the diagnostic criteria of DIC, which was established in 1988, is based on the values of the PT ratio, the plasma levels of fibrinogen, FDP, and the platelet count [7]. This diagnostic criteria is of general use in Japan. However, early diagnosis and treatment of DIC recently have become the focus of many clinical investigations. Although a definite criteria for diagnosis of DIC has not been established as yet, the detection of sFM has been suggested as a potential marker for the early diagnosis of DIC [18]. sFM ELISA, which detected the N-terminus of fibrin-α-chain [19], is considered to reflect the early stage of DIC. The plasma levels of TAT [10] and prothrombin fragment F1+2 [12] reflect intravascular thrombin generation, but do not directly reflect microthrombi formation. Plasma sFM levels reflect the intensity of fibrinogen-converting activity of thrombin. Plasma cross-linked fibrin degradation products (XDP; D-dimer) is considered to be the most useful marker for diagnosis of DIC and pre-DIC. However, plasma D-dimer can derive not only from intravascular fibrin but also from extravascular fibrin.

The change of the PT ratio was not significant 3 days before the onset of DIC, suggesting that the PT ratio is not a useful marker for the diagnosis of pre-DIC. Plasma fibrinogen levels were significantly reduced 5 days before the onset of DIC; these levels were higher than the normal range but they were not useful for the diagnosis of pre-DIC. The positive rate of the PT ratio and fibrinogen were low in pre-DIC, and very low in non-DIC states. Indeed, the specificity of the PT ratio and fibrinogen for the diagnosis of DIC was high but their sensitivity was very low [13]. In nonleukemic patients, the plasma levels of FDP before the onset of DIC were moderately high; these levels were significantly high at the onset of DIC. However, in the nonleukemic group, the positive rate of FDP was already high in the non-DIC state. In nonleukemic patients, the platelet count was gradually decreased, and its positive rate was gradually high before the onset of DIC, and moderately high in non-DIC patients. These markers were reported to be sensitive but not specific [13], and thus they are not

TABLE III. Hemostatic Molecular Markers in Pre-DIC†

		Day				
		−7	−5	−3	−1	0
D-dimer (ng/ml)	L	1387 ± 999	1696 ± 1134	1677 ± 1189	2435 ± 1557*	4439 ± 2297**
	N	1759 ± 1015	2110 ± 1310	1807 ± 1249	2100 ± 1480	4677 ± 2847**
sFM (μg/ml)	L	44.7 ± 57.7	86.7 ± 68.4*	90.1 ± 39.7**	133 ± 108**	311 ± 196**
	N	118 ± 27.3	140 ± 136	158 ± 106	203 ± 127**	340 ± 252**
TAT (ng/ml)	L	9.9 ± 6.1	11.1 ± 7.6	18.3 ± 10.2*	20.2 ± 11.7**	39.6 ± 19.0**
	N	22.6 ± 12.9	27.3 ± 15.7	24.6 ± 14.6	23.6 ± 12.7	39.6 ± 27.5**
PPIC (μg/ml)	L	1.3 ± 1.2	1.9 ± 3.2	2.1 ± 2.5	2.2 ± 2.0	4.6 ± 5.2**
	N	3.6 ± 3.6	3.1 ± 3.6	1.7 ± 1.6	2.7 ± 2.2	2.9 ± 2.8

†DIC, disseminated intravascular coagulation; sFM, soluble fibrin monomer; TAT, thrombin–antithrombin complex; PPIC, plasmin–plasmin inhibitor complex; L, leukemia; N, nonleukemia.
*$P < 0.05$.
**$P < 0.01$, compared with −7 day.

TABLE IV. Plasma TF, PAI-I, and TM Levels in Pre-DIC†

	Day				
	−7	−5	−3	−1	0
TF (pg/ml)	220 ± 54	276 ± 248	288 ± 86	246 ± 45	252 ± 82
PAI-I (ng/ml)	20.9 ± 16.6	25.5 ± 15.4	32.9 ± 25.0	34.1 ± 5.5	70.2 ± 66.7
TM (ng/ml)	3.5 ± 1.5	3.7 ± 1.8	4.0 ± 2.1	6.5 ± 5.4*	13.1 ± 9.6**

†TF, tissue factor; PAI-I, plasminogen activator inhibitor-I; TM, thrombomodulin; DIC, disseminated intravascular coagulation.
*$P < 0.05$.
**$P < 0.01$, compared with −7 day.

useful for the diagnosis of pre-DIC. The plasma level of antithrombin is reduced in DIC patients with sepsis [20]; plasma antithrombin levels did not change significantly before the onset of DIC in patients with or without leukemia; these markers were significantly reduced in DIC patients without leukemia. Plasma D-dimer, sFM, TAT, and PPIC levels were high before the onset of DIC. In leukemic patients, the plasma levels of sFM on day 5, those of TAT on day 3, and D-dimer on day 1 were significantly increased before the onset of DIC. In nonleukemic patients, only D-dimer, sFM, and TAT levels were increased significantly 7 days before the onset of DIC compared with values in non-DIC patients. The positive rate of TAT and PPIC were high during the pre-DIC, but were also high in the non-DIC state. The positive rate of sFM and D-dimer were low in non-DIC and increased gradually during the pre-DIC state. Hemostatic molecular markers such as TAT, D-dimer, and sFM might be effective for the diagnosis of DIC, although their cutoff values for diagnosis of DIC or pre-DIC were different between leukemic patients and nonleukemic patients. Elevated TF is considered one of the most important causes in DIC [15], although plasma TF levels were not significantly changed before the onset of DIC. Plasma levels of TF pathway inhibitor, which is an inhibitor of tissue factor and Fxa, has been reported to increase during the course from pre-DIC to DIC [21]. Plasma PAI-I and TM levels are markedly increased in DIC patients with organ failure [14], and the plasma TM levels are increased 1 day before the onset of DIC. These

TABLE V. Hemostatic Markers at −7 Day Before Onset of DIC and Non-DIC†

		−7 Day before onset of DIC	Non-DIC
PT ratio	L	1.10 ± 0.12	1.22 ± 0.11
	N	1.16 ± 0.17	1.14 ± 0.20
Fibrinogen (mg/dl)	L	326 ± 165	300 ± 149
	N	321 ± 164	343 ± 157
FDP (μg/ml)	L	11.1 ± 7.0	11.9 ± 7.8
	N	29.4 ± 34.0	23.2 ± 19.8
PLT ($\times 10^4/\mu l$)	L	5.5 ± 4.8	6.2 ± 5.6
	N	17.7 ± 10.6	14.5 ± 9.6
Antithrombin (%)	L	87.2 ± 26.2	90.1 ± 21.1
	N	77.4 ± 24.0	72.8 ± 28.5
D-dimer (ng/ml)	L	1387 ± 999	1120 ± 1187
	N	1759 ± 1015*	1340 ± 1495
sFM (μg/ml)	L	44.7 ± 57.7	58.9 ± 61.8
	N	118 ± 27.3**	62.4 ± 31.4
TAT (ng/ml)	L	9.9 ± 6.1	15.5 ± 17.6
	N	22.6 ± 12.9*	14.0 ± 15.3
PPIC (μg/ml)	L	1.3 ± 1.2	1.9 ± 2.2
	N	3.6 ± 3.6	1.4 ± 1.5

†DIC, disseminated intravascular coagulation; PT, prothrombin time; FDP, fibrin degradation products; sFM, soluble fibrin monomer; TAT, thrombin–antithrombin complex; PPIC, plasmin–plasmin inhibitor complex; L, leukemia; N, nonleukemia.
*$P < 0.05$.
**$P < 0.01$, compared with non-DIC.

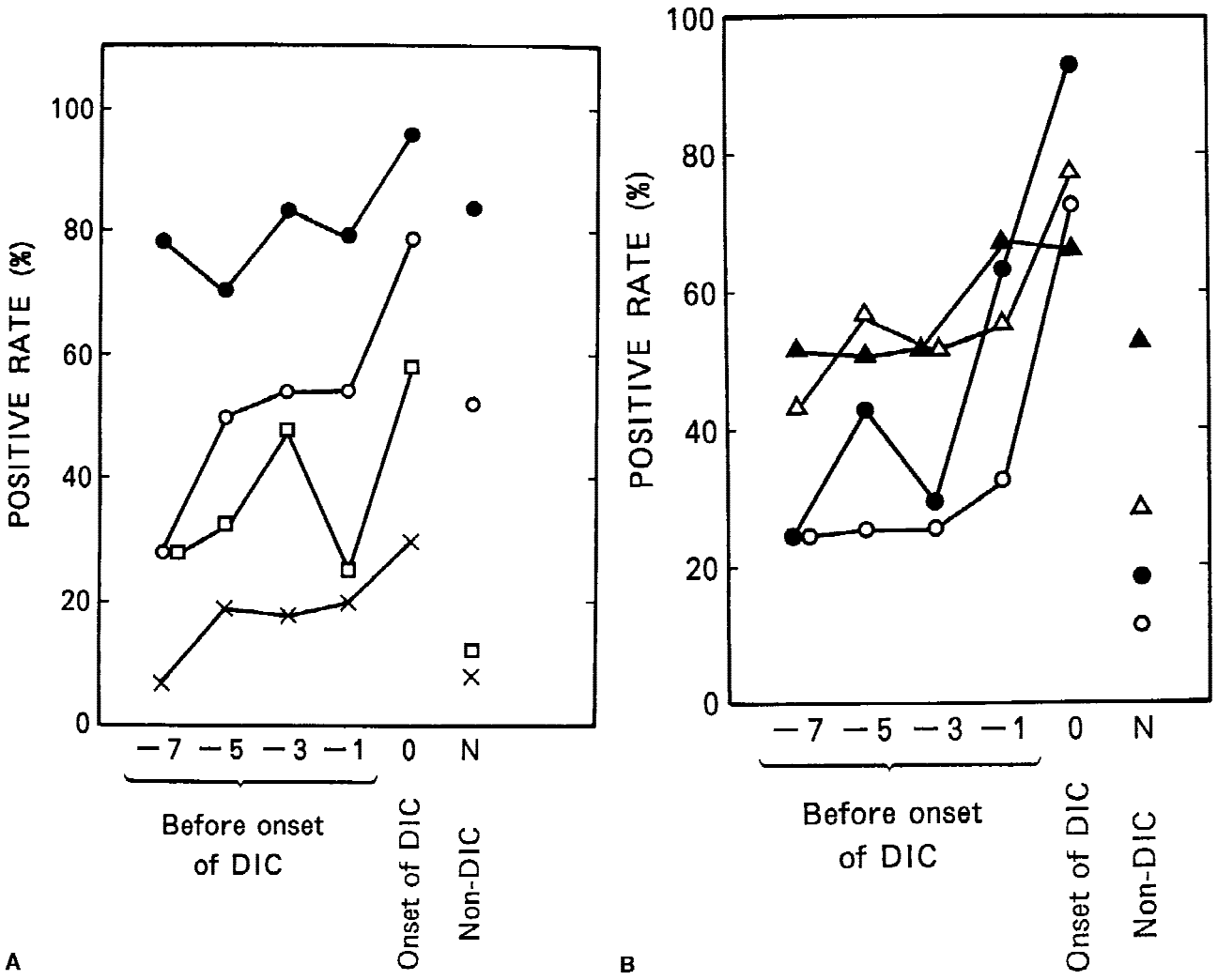

Fig. 1. A: Positive rate of FDP, PT, fibrinogen, and platelet count in DIC patients before the onset of DIC. ●, FDP; ○, platelet count; □, fibrinogen, X, PT ratio. B: Positive rate of D-dimer, TAT, PPIC, and sFM in DIC patients before the onset of DIC. ●, D-dimer; ○, sFM; ▲, PPIC; △, TAT.

finding suggest that vascular endothelial cell injury occurs before the onset of DIC.

The results of this study suggest that hemostatic molecular markers such as sFM, D-dimer, and TAT are useful for the diagnosis of pre-DIC, although their cutoff values were different among various diseases.

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